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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
ZARA, JANE J	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/701,007
Filing Date: November 04, 2003
Appellant(s): ALLERSON ET AL.

Jane E. Inglese
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4-29-10 appealing from the Office action mailed 7-30-09.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Application No. 10/860,265, Appeal Brief filed 4-30-10.

Application No. 11/054,848, Appeal Brief filed 4-30-10.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

The claims pending in the application are 34, 37, 38, 49, 53-62, 72, 74-78, 94-96, and 104.

Claims 34, 37, 38, 49, 53-62, 72, 74-78, 94-96, and 104 stand rejected and are the subject of this appeal.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

NEW GROUND(S) OF REJECTION

There are no new grounds of rejection.

WITHDRAWN REJECTIONS

There are no withdrawn grounds of rejections.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

US 2004/0180351	Giese et al.	September - 2004
US 2003/0143732	Fosnaugh et al.	July - 2003
US 2003/0206887	Morrissey et al.	November - 2003
6,232,036	Arnold et al.	July - 2001
US 2005/0142535	Damha et al.	June - 2005
6,133,246	McKay et al.	October - 2000

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Elbashir, S.M. et al., *Functional anatomy of siRNAs for mediating efficient RNAi in Drosophila melanogaster embryo lysate*, EMBO J., Vol. 20, No. 23, pages 6877-6888 (2001).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 34, 37, 38, 49, 53-62, 72, 74-78, 94-96, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al (EMBO J., Vol. 20, No. 23, pages 6877-6888, 2001), Giese et al (US 2004/0180351), Fosnaugh et al (US 2003/0143732) and Morrissey et al (US 2003/0206887), the combination in view of the combined teachings of Arnold et al (USPN 6,262,036), Damha et al (US 2005/0142535)

and McKay et al (USPN 6,133,246) for the reasons of record set forth in the Office action mailed 7-30-09.

Claims 34, 37, 38, 49, 53-62, 72, 74-78, 94-96, and 104 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 36, 44, 46-49, 52-64, 74-80, 93, 98-100 and 106 of copending Application No. 10/860,265 for the reasons of record set forth in the Office action mailed 3-26-07.

Claims 34, 37, 38, 49, 53-62, 72, 74-78, 94-96, and 104 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35-63 of copending Application No. 11/054,848 for the reasons of record set forth in the Office action mailed 3-26-07.

(10) Response to Argument

Claims 34, 37, 38, 49, 53-62, 72, 74-78, 94-96, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al (EMBO J., Vol. 20, No. 23, pages 6877-6888, 2001), Giese et al (US 2004/0180351), Fosnaugh et al (US 2003/0143732) and Morrissey et al (US 2003/0206887), the combination in view of the combined teachings of Arnold et al (USPN 6,262,036), Damha et al (US 2005/0142535) and McKay et al (USPN 6,133,246) for the reasons of record set forth in the Office action mailed 7-30-09.

The claims are drawn to compositions comprising chemically synthesized siRNA oligonucleotides comprising an alternating motif having a 2'-F and a β-D-

deoxyribonucleoside as alternating nucleosides, wherein one or both of the self complementary strands of the siRNA molecule comprise this alternating motif, and which siRNA optionally further comprise, in addition to the above alternating motif, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps, optionally including inverted deoxy abasic moieties, or optionally comprise one or more terminal overhanging nucleobases.

Elbashir et al (EMBO J., vol. 20, No. 23, pages 6877-6888, 2001) (*hereinafter* "Elbashir") teach methods of target gene inhibition in embryo lysates comprising siRNA molecules comprising 2'-deoxy and 2'- substitutions. Elbashir teach the means and routine methods to obtain a correlation between the placement of 2'-substitutions on the siRNA oligonucleotides and the retention of siRNA activity (see esp. the abstract on p. 6877, fig. 8 and text on p. 6885).

Giese et al (US 2004/0180351) (*hereinafter* "Giese") teach siRNA molecules comprising alternating 2' substituted nucleobases with enhanced stability and prolonged inhibitory capacity compared to unmodified siRNA molecules, and optionally additionally comprising terminal overhanging nucleobases (see esp. Fig. 12, 14; paragraphs 0124, 0182, example 11, e.g., paragraphs 0189-0193, claim 18).

Fosnaugh et al (US 2003/0143732) (*hereinafter* "Fosnaugh") teach various configurations of 2'-modifications, including 2'-fluoro or 2'-methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide

linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini, and the routine experimentation involved in testing the effect of arrangements of these different modifications on siRNA ability to bind to and inhibit target gene expression in the presence of RISC. Fosnaugh also teaches compositions comprising modified and unmodified siRNAs in the presence of RISC for target gene inhibition see p. 1, 3-4, 6-9, p. 16 and figures 4 and 5, claim 30).

Morrissey et al (US 2003/0206887) (*hereinafter* "Morrissey") teach various ways of designing and optimizing 2'- modifications on siRNA, including 2'-fluoro or methoxyalkyl groups of various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini, and the effect of various motifs or arrangements of these 2'substitutuents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in compositions further comprising RISC (see fig. 4 and 5, page 1, right col., p. 6, right col., p. 9, p. 20-21, claims 20-25).

The primary references do not teach an alternating motif having a 2'-F and a β-D-deoxyribonucleoside as alternating nucleosides, wherein one or both of the self -complementary strands of the siRNA molecule comprise this alternating motif.

Arnold et al (USPN 6,262,036) (*hereinafter* "Arnold") teach the modification and testing of inhibitory oligonucleotides comprising alternating 2'- -D-deoxynucleosides with 2'-modified nucleosides, and the introduction of these modifications for enhancing target binding stability (see esp. example 34, col. 48-50).

Damha et al (US 2005/0142535) (*hereinafter* "Damha") teach the modification and testing of inhibitory activity of antisense oligonucleotides comprising alternating 2'- -D-deoxynucleosides with 2'-modified nucleosides in antisense oligonucleotides for enhancing target binding by antisense molecules for the binding and inhibition of target gene expression.

McKay et al (USPN 6,133,246) (*hereinafter* "McKay") teach numerous motifs and combinations of modified residues within antisense oligonucleotides, including the incorporation of 2'-modified sugars which include 2'-fluoro, 2'-bromo, 2'-O-alkyl groups, modified nucleobases, modified internucleotide linkages, 2'- -D-deoxynucleosides and combinations thereof, as well as the optimization of modifications for maximizing target binding, cellular uptake and oligonucleotide stability (see esp. col. 7-12; Tables 4-26, esp. Tables 11 and 12, and Table 26).

It would have been obvious to incorporate various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini into siRNA molecules for enhancing their target binding and stability, yet minimizing inactivation of the siRNA ability to inhibit target gene expression because Elbashir, Fosnaugh and Morrissey all teach the designing

and testing of various arrangements of modified siRNA for their ability to inhibit target gene expression.

It would have been obvious to design and test the instantly claimed alternating motif having a 2'-F and a β-D-deoxyribonucleoside as alternating nucleosides, wherein one or both of the self complementary strands of the siRNA molecule comprise this alternating motif because Giese teaches increased siRNA stability from nucleases and increased and sustained target gene inhibition using siRNA with alternating 2' modified residues. The features of enhanced stability, enhanced target binding, enhanced cellular uptake had been taught previously for oligonucleotides comprising 2' modified residues, the assays for siRNA activity were well known in the art, and the techniques for incorporating the claimed modifications were also well known in the art at the time of the instant invention and would have involved routine experimentation. Alternating modified residues have been assayed in all types of inhibitory oligonucleotides, including in antisense and siRNA molecules and have been taught as feasible design choices for enhancing inhibitory oligonucleotide stability, cellular uptake, target binding and inhibitory capabilities.

One of ordinary skill in the art would have incorporated alternating 2'- -D-deoxynucleosides with 2'-modified nucleosides into RNAi molecules because it was well known at the time of the invention that such alternating modifications enhanced target binding stability of the antisense oligonucleotides for their target regions, as taught previously by Arnold and Damha, and it was also well known at the time that the antisense strand of the siRNA molecule must also target and bind the target gene prior

to target gene inhibition. One of ordinary skill would have expected that the incorporation of these modifications are optimized using routine experimentation because Damha, McKay and Arnold all teach optimization experiments where antisense oligonucleotides comprising an array of different combinations of these well known modifications are tested for their ability to target and bind target genes and inhibit their expression, the ability to incorporate the modifications claimed were well known in the art, and testing different motifs was very routine at the time the instant invention was made.

One of ordinary skill in the art would have been motivated to combine the teachings of Elbashir, Fosnaugh and Morrissey, as applied to modifying and testing the activity of siRNA, with the teachings by McKay, Damha and Arnold regarding the incorporation of modifications into inhibitory antisense oligonucleotides, for enhancing their ability to bind a target gene and for their ability to enhance oligonucleotide stability, and design and test the motifs instantly claimed, including alternating 2'- -D-deoxynucleosides with 2'-modified nucleosides. One of ordinary skill in the art would have expected that the siRNA molecules, modified with the various and appropriate configurations would provide target gene cleavage in the presence of an appropriate target gene sequence and in the presence of appropriately modified siRNA. One of ordinary skill in the art would have produced various motifs as a matter of design choice and optimizing 2'- modified motifs within the siRNA while maintaining its siRNA activity would have been a matter of design choice after testing various modifications and their

combinations in a manner previously done by many in the art for antisense, such as McKay and Arnold.

One of ordinary skill in the art would have designed and tested such modification motifs because it was well known in the art at the time of the instant invention that incorporation of 2'-O-methoxy alky or 2'-deoxy, or 2'-fluoro modifications at appropriate positions within the siRNA allows for enhanced oligonucleotide stability, target binding and the trigger of target gene degradation by RISC. One of ordinary skill in the art would also have been motivated to incorporate 5', and/or 3' caps, including abasic and inverted abasic nucleotide or other terminal well known caps because these modifications were well known in the art to protect oligonucleotides from degradation, as taught previously by Morrissey.

Argument

Applicant's arguments filed 4-29-10 have been fully considered but they are not persuasive. Applicant argues that no credible reasons have been provided as to why one of ordinary skill in the art would have combined particular aspects of the cited references to arrive at the claimed compositions. Applicant asserts that hindsight has been used to pick and choose elements from vast, unpredictable and sometimes contrary art to arrive at the claimed subject matter, the claimed invention has not been considered as a whole and therefore a *prima facie* case of obviousness has not been established.

Contrary to Applicant's assertions, the invention as a whole has been properly considered. The invention involves the systematic incorporation of well known modifications routinely used to improve stability, target binding, and cellular uptake of RNA molecules which act as inhibitory oligonucleotides. Applicant's assertions that the elements from which to choose are vast and unpredictable is simply not true. The references relied upon in the instant obviousness rejection are directed to a finite set of possibilities. The modifications claimed were historically designed for antisense, and it should be noted that siRNA molecules also involve an antisense strand which must specifically bind to a target gene. The fact that siRNA and RNase-activating antisense involve different mechanisms for target gene inhibition does not make optimization of siRNA modifications insurmountable. It merely requires the systematic testing of the modifications' effects on siRNA activity. The modifications instantly claimed did not originate with siRNA, they developed in the antisense field and have now logically been applied to the siRNA field. The routine testing and optimization of well known patterns such as alternating motifs of 2' modified residues, as well as the incorporation of deoxy residues, and even of gapmers in some instances, had started surfacing in the literature shortly after Fire's discovery of siRNA. They are a logical extrapolation of the antisense field. It is no surprise that the instantly claimed motif was found to provide some advantages over unmodified siRNA. The instantly claimed motif is an obvious design choice that was easily synthesized, and easily tested for siRNA activity.

Applicant argues that the prior art of Elbashir, Fosnaugh, Morrissey, Arnold, Damha and McKay fail to teach or suggest the particular pattern of chemical

modifications presently claimed, and instead merely provide generalized teachings regarding chemical modification of nucleic acids. Applicant also argues that Elbashir provides no guidance as to which modifications at what positions may be tolerated, and the results taught by Elbashir fall far short of teaching a correlation between placement of modifications in siRNA duplexes and retention of RNAi activity. Applicant argues that Giese does not specifically describe siRNAs with alternating 2' modified residues, but instead teaches modifications of both strands comprising 2'-O-methyl modified nucleotides alternating with unmodified ribonucleotides, and fails to teach incorporating β-D-deoxyribonucleosides as instantly claimed.

Applicant additionally argues that the prior art does not teach ways of designing and optimizing such configurations as instantly claimed, but instead describes vast genii of siRNA molecules and broadly discusses possible chemical modifications for the molecules. Applicant argues, for instance, the Fosnaugh and Morrissey provide no guidance as to which positions might be critical for siRNA mediated inhibition, and that the pattern of modifications taught by them depends entirely upon the base sequence of the particular oligonucleotide, and they fail to teach alternating motifs. Applicant also argues that the secondary references describe oligonucleotides utilizing RNase H-dependent mechanisms and such different mechanisms would not provide reasons to believe that the modifications or motifs useful for oligonucleotides utilizing RNase-H dependent mechanisms would have been useful for siRNA oligonucleotides. Applicant asserts that the references relied upon actually demonstrate the unpredictability and absence of meaningful guidance in designing such molecules. Applicant also argues

that the teachings of Damha, McKay and Arnold lack any teaching that would facilitate the design of siRNAs, and that the significant differences in the biological mechanisms used by RNase H (antisense) and RISC (siRNA) have been trivialized, and that the instant rejection for obviousness relies upon an obvious to try standard combined with a reasonable likelihood of success, and that both of these prongs have not been established..

Contrary to Applicant's assertions, the reliance upon the teachings of Elbashir, Giese, Fosnaugh, Morrissey, Arnold, Damha and McKay do indeed render the instantly claimed invention obvious. The methods of incorporating all of the modifications into oligonucleotides as instantly claimed were well known in the art for at least 15 years. What's more, the assays for measuring siRNA inhibitory activity, and ways of determining siRNA stability were also well known in the art, involving routine techniques used widely by investigators in the field of molecular biology.

Giese taught the routine optimization of incorporating alternating motifs on the different strands of siRNA, the retention of sustaining gene silencing activity, and enhanced resistance to nuclease degradation. Morrissey is very clear about the motivation to correlate siRNA activity (as a result of stability, target binding and inducing target gene cleavage) with the incorporation of various well known oligonucleotide modifications, which are tested as incorporated on either of the two strands of an siRNA molecule (see paragraph 0050):

> Non-limiting examples of such chemical modifications include without limitation phosphorothioate internucleotide linkages, 2'-deoxyribonucleotides, 2'-O-methyl ribonucleotides, 2'-deoxy-2'-fluoro ribonucleotides… and/or inverted deoxy abasic residues incorporation.

> These chemical modifications, when used in various siNA constructs, are shown to preserve RNAi activity in cells while at the same time, dramatically increasing the serum stability of these compounds…

And in paragraph 0052:

> In a non-limiting example, the introduction of chemically-modified nucleotides into nuclei acid molecules will provide a powerful tool in overcoming potential limitations of in vivo stability and bioavailability inherent to native RNA molecules that are delivered exogenously.

Elbashir taught the means and motivation to test the effect of various modifications on siRNA activity. In the bridging paragraph between pages 6881-6882, Elbashir teaches that substitution of 8 out of 42 nucleotides of the siRNA duplex did not lead to loss of activity, and that SiRNA with 2'-deoxynucleotides produced "significantly active siRNAs". This is in contrast to complete substitution with 2'-O-methyl, and it is in contrast to complete substitution with 2'-deoxy residues, which led to abolition of RNAi activity when studied by Elbashir.

And on page 6884, second full paragraph, some of the "most efficient siRNA duplexes" included 2'-deoxy modifications. So, contrary to Applicant's assertions, the teachings of Elbashir, Fosnaugh, and Morrissey emphasize the importance of routinely testing the placements and types of modifications on siRNA, and the effects of these modifications and their locations on the siRNA molecule on oligonucleotide stability, target binding and the inhibitory capabilities of siRNA – using very routine methods.

What's more, Giese, Arnold and Damha taught the well known motif of alternating modified residues, and how to balance the advantages provided by incorporating these modifications with the particular requirements of the inhibitory

mechanism utilized by the inhibitory oligonucleotides. This prior art taught the incorporation of 2'- -D-deoxynucleosides with 2'-modified nucleosides in oligonucleotides for enhancing target binding and stability. Arnold and Damha both stressed the importance of having some deoxyribonucleosides on an antisense strand for successful oligonucleotide binding to the target nucleic acid molecules, which deoxyribonucleosides are in a 2'-endo conformation, as opposed to the 3'-endo conformation of ribonucleosides.

On the other hand, Arnold also taught lower binding affinity toward complementary target strands of 2-deoxyribonucleosides compared to 2'-substituted nucleosides. These features are important to balance for effective target gene inhibition using both antisense mediated and siRNA mediated gene inhibition. Both mechanisms require efficient target binding by the inhibitory oligonucleotides. Therefore one of ordinary skill in the art would have been motivated to test obvious combinations of modified residues, such as alternating residues of 2'-Fluoro and 2-deoxy nucleosides on siRNA oligonucleotides to see if these motifs would provide for enhanced target gene cleavage. Such an example of routine experimentation is taught by Giese with respect to alternating motifs on sense and antisense strands of active siRNA molecules. The means for incorporating such motifs required routine experimentation at the time of the instant invention, and assaying for target inhibition in the presence of siRNA bearing different motifs required routine assays well known in the art.

In addition, the effect of various arrangements of different modifications on siRNA ability to bind to and inhibit target gene expression in the presence of RISC was taught

by many in the art, including Giese and Fosnaugh, whose modified siRNAs included various motifs and configurations of 2'-modifications, including alternating motifs, and including the incorporation of fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprised, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprised 3'-and/or 5'-terminal caps and optionally included inverted deoxy abasic moieties on the termini. The effect of different arrangements of these various modifications on siRNA ability to bind to and inhibit target gene expression in the presence of RISC was therefore taught previously by Fosnaugh.

Morrissey also taught various ways of designing and optimizing 2'- modifications on siRNA, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini. And Morrissey taught the effect of various motifs or arrangements of 2'-substitutuents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in compositions further comprising RISC.

Elbashir, Giese, Fosnaugh and Morrissey taught the routine experimentation involved in designing and testing arrangements of modified residues on siRNA for their ability to inhibit target gene expression, and the importance of balancing the introduction of stabilizing and other modifications into the antisense strand with the minimal requirements of RISC recognition and target cleavage. The testing of modified siRNA molecules for inhibitory activity required routine experimentation of various design

choices, nothing more. All of the instantly claimed modifications were well known in the art, and researchers in the art routinely assayed different configurations of modifications for antisense, ribozyme and siRNA mediated inhibition. McKay taught numerous motifs and combinations of modified residues within antisense oligonucleotides, including the incorporation of 2'-modified sugars which include 2'-fluoro, 2'-bromo, 2'-O-alkyl groups, modified nucleobases, modified internucleotide linkages, 2'- -D-deoxynucleosides and combinations thereof, as well as the optimization of modifications for maximizing target binding, cellular uptake and oligonucleotide stability (see esp. col. 7-12; Tables 4-26, esp. Tables 11 and 12, and Table 26).

McKay is relied upon in the instant 103 rejection for teaching various combinations of modified residues incorporated into antisense oligonucleotides, including 2'-modified nucleosides which include the incorporation of 2'-fluoro, 2'-bromo, 2'-O-alkyl groups, as well as the incorporation of modified nucleobases, internucleotide linkages, 2'- -D-deoxynucleosides, and combinations thereof. McKay is therefore properly relied upon for the routine experimentation of incorporating these well known modifications into various motifs, and is relied upon for teaching the well known effects of these modifications, including enhancing target binding, cellular uptake and oligonucleotide stability.

Giese, Fosnaugh and Morrissey both taught effects on gene silencing activity after incorporating various motifs and configurations of 2'-modifications into siRNA molecules, including the incorporation of fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprised phosphorothioate

internucleotide linkage modifications, 3'-and/or 5'-terminal caps, and inverted deoxyabasic terminal moieties. Giese, Fosnaugh and Morrissey taught the routine experimentation involved in testing the effects of different arrangements of these various, well known modifications on siRNA's ability to bind to and inhibit target gene expression in the presence of RISC. Giese, Fosnaugh and Morrissey also are relied upon for teaching compositions comprising modified and unmodified siRNAs (and RISC) for target gene inhibition.

Damha taught alternating 2'- -D-deoxynucleosides with 2'-modified nucleosides in inhibitory oligonucleotides, and the effects of this configuration on various properties of inhibitory oligonucleotides, including effects on target binding by antisense molecules and their inhibition of target gene expression. Damha taught the effects of various motifs or configurations of modified residues on the antisense oligonucleotides' abilities to inhibit target expression, particularly on their ability to elicit RNAse H cleavage of a target strand.

Giese, Arnold, Damha all taught the well known motif of alternating modified residues on inhibitory oligonucleotides, including the incorporation of 2'- -D-deoxynucleosides with 2'-modified nucleosides in oligonucleotides for enhancing target binding and stability. Arnold compared the inhibitory capabilities of inhibitory oligonucleotides in the presence of modified and unmodified internucleotide linkages. Arnold taught inhibitory oligonucleotides comprising alternating 2'- -D-deoxynucleosides with 2'-modified nucleosides, and the introduction of these modifications for enhancing target binding stability (see esp. example 34, col. 48-50).

So, contrary to Applicant's assertions, the motif comprising alternating 2'- -D-deoxynucleosides with 2'-modified nucleosides was well known in the art, the testing of various configurations of the modifications claimed on siRNA activity required routine experimentation well known in the art. And the teachings of Giese, Elbashir, Fosnaugh, Morrissey, Arnold, Damha and McKay, regarding the advantages of modifying oligonucleotides to enhance stability and target binding, while retaining siRNA or antisense activity, actually provide a reasonable expectation of success of finding the instantly claimed design choice of modified oligonucleotides which retain siRNA activity, and therefore render the instant invention obvious. Since alternating motifs of well known modifications were well established design choices, the instant motif would have been a logical design choice to test for potentially enhancing siRNA binding, activity, and/or stability, and not the result of an infinite possibility of choices, as suggested by Applicant.

Giese, Elbashir, Fosnaugh and Morrissey all taught the designing and testing of various arrangements of modified residues on siRNA for their ability to inhibit target gene expression - using routine experimentation for both the incorporation of these well known modifications, and assaying different configurations for siRNA mediated inhibition. One of ordinary skill in the art would have incorporated 2'- -D-deoxynucleosides and 2'-modified nucleosides, including the well known 2'-fluoro modification, into siRNA molecules because these modifications were well known in the art to offer potential stabilizing, target binding and cellular uptake advantages over unmodified residues at the time of the instant invention. An alternating motif would have

been a logical configuration or design choice to incorporate into and siRNA molecule, and testing the effect of such a well known configuration would have involved routine experimentation at the time of the instant invention.

For these reasons, the instant invention as a whole would have been *prima facie* obvious to one of ordinary skill at the time it was made.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

/Jane Zara/
AU 1635

Conferees:

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1639

/Fereydoun G. Sajjadi/
Acting Supervisory Patent Examiner, AU 1635